Long-term global quality of life in patients treated for colorectal liver metastases

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Original article

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Background: **Surgical treatment of colorectal liver metastases has become increasingly aggressive. The influence of this more active surgical approach on patients' health-related quality of life (HRQoL) has hardly been evaluated. This study investigated the impact of surgical and systemic treatment on HRQoL in patients undergoing hepatic resection for colorectal metastases.**

Methods: **A total of 145 patients with colorectal liver metastases were entered prospectively into the study. Based on HRQoL values derived from the EuroQol – 5D, health summary measures were calculated to express the overall impact on four distinct clinical states. The HRQoL instrument was used at baseline, 3 and 6 weeks after surgery, and every 3 months thereafter for up to 3 years.**

Results: **Patients showed a clear deterioration in HRQoL in the first weeks after surgery, followed by a recovery to baseline levels at 3 months after potentially curative surgery. In contrast, a sustained decline was noted when initial surgery for colorectal liver metastases was considered futile and palliative chemotherapy was started immediately. Three years after initial surgery, there were distinct differences in HRQoL between patients with or without recurrence. The latter group still had HRQoL scores at baseline levels, whereas patients with tumour recurrence showed a significant deterioration in HRQoL. Remarkably, there was no decline in HRQoL in patients with recurrent disease who could be treated by secondary surgical intervention.**

Conclusion: **Superior overall HRQoL in the first 3 years after initial successful surgical intervention merits an aggressive surgical approach and intensive follow-up to detect recurrence early.**

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Introduction

Colorectal cancer is the third commonest cancer and the second most frequent cause of cancer-related death. Worldwide, approximately half a million people die from colorectal cancer every year[1]. Liver metastases develop in 40 per cent of all patients with colorectal cancer[2] and, if metastatic disease is limited to the liver, resection is the curative treatment of choice. Survival rates of 40–50 per cent for the first 5 years after initial treatment have been reported[3,4].

For many years, outcomes of medical treatments in cancer were expressed primarily in terms of survival and disease-free status. Changes in health policy have shifted the emphasis of health evaluation from traditional, easy-to-measure clinical indicators to more complex patient-based outcomes such as quality of life. Today, it is increasingly acknowledged that quality of life, or rather health-related quality of life (HRQoL), is an important additional outcome measure in the assessment of oncological surgery and systemic treatment[5–7].

Several studies have already addressed long-term HRQoL in primary colorectal cancer[8–11]. However, few data are available on HRQoL after surgery for metastatic colorectal cancer[12]. As contraindications for surgical treatment of metastatic disease are increasingly being abandoned and local ablative techniques are upcoming treatment modalities, an increasing number of patients are qualifying for aggressive treatment[13]. Although considered important in this context, data on HRQoL in this patient category are scarce in the current literature.

Most HRQoL instruments measure multiple domains (for example European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30) and are therefore commonly indicated as descriptive profile measures. In contrast, a distinguishing feature of a value-based HRQoL instrument is its potential to assign a single metric figure to a specific health status.

Such value-based HRQoL instruments produce outcomes that can be incorporated into health summary measures such as quality-adjusted life years (QALYs) and the Quality-adjusted Time Without Symptoms of disease and Toxicity of treatment (Q-TWiST). Health summary frameworks produce an outcome measure that combines the effects of health interventions on mortality and morbidity into a composite measure of health benefit[14].

The aim of this prospective study was to describe long-term HRQoL comprehensively by the use of health summary frameworks in patients undergoing surgical treatment of colorectal liver metastases.

Methods

Patients were enrolled in a prospective multicentre trial between May 2002 and February 2006. Four surgical departments with experience in liver surgery participated in this trial. Patients were required to have a history of proven colorectal cancer treated by surgical resection and suspicion of up to four potentially resectable colorectal liver metastases without evidence of extrahepatic metastatic disease on contrast-enhanced computed tomography and/or fluorodeoxyglucose–positron emission tomography. The study was approved by the ethics committees of all participating centres, and all patients provided written informed consent.

Laparotomy for hepatic resection was generally performed within 4 weeks after inclusion (range 1–7 weeks). Surgical treatment was performed only if it was deemed feasible to remove all liver lesions adequately. Resection of an isolated extrahepatic intra-abdominal lesion was performed, but further surgical treatment of any other extrahepatic disease discovered during laparotomy was carried out at the surgeon's discretion. After hepatic surgery, patients did not receive any standard (adjuvant) chemotherapy. Follow-up lasted for 3 years after the initial intervention.

None of the patients received preoperative chemotherapy. Chemotherapy was started only in the event of unresectable disease or tumour recurrence that was not amenable to surgical reintervention. During the study period systemic chemotherapy consisted of 5-fluorouracil, leucovorin and oxaliplatin as first-line and irinotecan as second-line treatment. From 2005, bevacizumab was added to the standard chemotherapy regimen.

Clinical management and perioperative findings were documented prospectively in standard case record forms. For assessment of HRQoL, futile laparotomy was defined as any laparotomy that did not result in surgical treatment of liver metastases, either because of extrahepatic disease or because liver involvement was too extensive and resection would lead to an insufficient liver remnant. Hence, patients were categorized in two groups: one in which surgery was considered curative (curative surgery group) and the other in which surgery was considered futile (non-curative group) because complete resection of all tumour lesions during laparotomy was not considered possible.

Health summary frameworks

The QALY was used as a health summary measure[15,16]. It comprises two key elements, which together express health, namely the quantity and the quality of life lived. Apart from the QALY, the Q-TWiST method was used as a particularly promising alternative approach to expressing the overall impact of medical interventions in the setting of cancer treatment[17,18]. The objective of the Q-TWiST method, similar to the QALY method, is to include patient mortality (survival) and HRQoL in a single analysis. However, in the Q-TWiST method HRQoL is expressed for a limited number of distinct clinical health states (see statistical analysis section for computational strategy).

Health-related quality-of-life instrument

The EuroQol – 5D (EQ-5D™; EuroQol Group, Rotterdam, The Netherlands), a widely applied and validated instrument, was used as a generic value-based HRQoL instrument. The EQ-5D™ encompasses five different domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression[19]. Each attribute is rated at three levels: no problems, some problems or severe problems. The EQ-5D™ index or value is obtained by applying predetermined weights to the five

domains derived from the general public. This results in a society-based quantification of the respondents' health status or HRQoL on a scale of 0 (dead) to 1 (perfect health)[20]. Furthermore, the respondents were asked to rate their overall HRQoL on a visual analogue scale (EQ-5D™ VAS) consisting of a vertical line ranging from 0 (worst imaginable health status) to 100 (best imaginable), representing the patients' perspective. As these two measures (society based and patient based) are expressed on an absolute scale capturing the whole continuum of HRQoL, differences of 1–2 per cent can be considered as clinically important. Baseline EQ-5D™ forms were completed in hospital, and subsequent forms were sent to the patient's postal address 3 and 6 weeks after surgery, and every 3 months thereafter for the next 3 years. If forms were not returned within 2 weeks, a telephone or written reminder was sent.

Statistical analysis

For Q-TWiST analyses all patients were distributed over four categories, representing the main clinical states of patients with colorectal cancer after initial treatment of liver metastases: death, the state after non-curative surgery, the state after curative surgery with recurrent disease, and the disease-free state after curative surgery. For each state, the proportion of patients was calculated for the entire follow-up period of 3 years. Patients could shift between states in a certain order (*Fig. 1*). Next, mean HRQoL values were determined for each of the four clinical states based on the EQ-5D™ measures. In the Q-TWiST, the element of time was expressed as the interval between two measurements. Finally, for each clinical state the mean duration was multiplied by the corresponding mean HRQoL value and the proportion of patients. This resulted in the number of QALYs accumulated for each clinical state during 3 years of follow-up. One-way ANOVA was applied to test for differences between groups at various measurement points (*ad hoc* multiple comparison test; Scheffé test). All statistical analyses were performed with SPSS® statistical software version 17.0 (SPSS, Chicago, Illinois, USA).

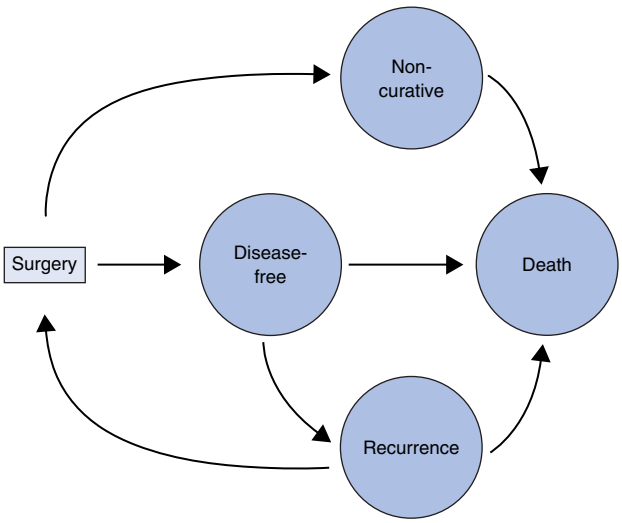


Fig. 1 State transition diagram for patients in possible clinical health states

Results

A total of 145 patients were included in the study. Seven patients were excluded from further analysis because final histology after laparotomy demonstrated the presence of benign liver lesions without evidence of metastatic colorectal cancer. Thus, 138 patients underwent laparotomy for potentially curative resection of proven liver metastases. The general demographics (sex ratio, mean age) and tumour characteristics (primary cancer site, tumour status, node status) of this group are summarized in *Table 1*. Before intervention, 136 (98·6 per cent) of the 138 patients completed the EQ-5D™ instrument; this group was analysed prospectively. After 3 years the overall response rate was 90·8 per cent (1852 forms of 2040 possible responses).

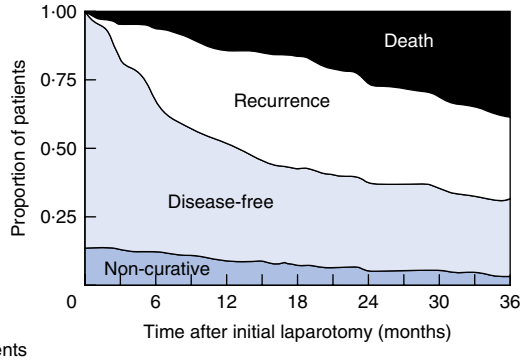
Distribution of the four clinical states

The four clinical groups representing the main clinical status options (death, non-curative surgery, curative surgery with recurrent disease, and curative surgery with disease-free status) and their distribution over time are

Table 1 Demographics and tumour characteristics

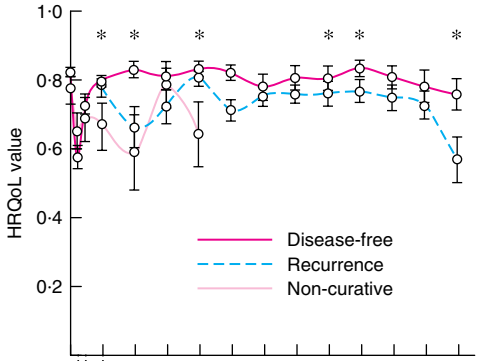
	No. of patients*
Mean (range) age (years)	63 (33–80)
Sex ratio (F : M)	44 : 94
Node status of primary tumour	
N0	60
N+	78
Disease-free interval (months)†	
≤ 12	57
> 12	81
No. of hepatic tumour(s)‡	
1	82
2–4	56
Median (range) size of largest lesion (mm)	35 (6–160)

*Unless indicated otherwise. †Interval between diagnosis of primary tumour and hepatic metastases. ‡As seen on preoperative computed tomography.



No. of patients													
Death	0	7	9	14	20	21	23	29	36	39	43	48	53
Recurrence	0	16	35	44	45	53	55	52	49	47	45	44	41
Disease-free	117	95	75	63	59	50	48	56	44	43	40	38	38
Non-curative	19	18	17	15	12	12	10	9	7	7	7	6	4

Fig. 2 Proportion of patients in each of the four clinical states over time in the first 3 years after initial hepatic resection for colorectal metastases (patients may have moved from one state to another over the course of the study)



No. of patients													
Disease-free	117	103	97	91	70	60	54	43	43	41	38	38	35	30	34
Recurrence	0	2	5	16	34	37	41	45	44	44	43	39	37	33	36
Non-curative	19	17	17	16	16	13	12	10	10	6	7	6	5	5	4

Fig. 3 Mean index value of patients' health calculated by the EuroQol – 5D for each clinical health state in the first 3 years after initial resection of hepatic colorectal metastases. The area under the curve corresponds to the number of quality-adjusted life years. Error bars represent standard errors. HRQoL, health-related quality-of-life. Asterisks indicate statistically significant effects ($P < 0{\cdot}050$), reported only if the number of observations exceeded ten (one-way ANOVA)

depicted in *Fig. 2*, representing the Q-TWiST. The states 'disease-free' and 'non-curative' were the main groups in the first few months. In the course of the study, the percentage of patients with 'recurrence' and 'death' obviously increased. In total, 117 patients (86·0 per cent) underwent successful surgical intervention (curative group), whereas 19 (14·0 per cent) had a non-curative laparotomy because of inoperable disease at the time of surgery. Disease-free survival of all 136 patients at 2 and 3 years was 32·4 per cent (44 of 136) and 27·9 per cent (38 of 136) respectively. The median time to disease recurrence was 8·5 (range 0–75) months. For patients with recurrent disease and no option for surgical reintervention, chemotherapy was started at a median of 12·0 (range 1–36) months after hepatic resection.

Health-related quality of life associated with the four clinical states

Three weeks after surgery, all patient groups showed a clear decrease in HRQoL, as expressed in the EQ-5D™ values. Thereafter, HRQoL values for three of the clinical groups showed distinct patterns over time (death has a value of 0 by definition). In general, disease-free patients had the best HRQoL, whereas patients who had undergone non-curative surgery were doing worse than patients with recurrent disease (*Fig. 3*). Statistically significant overall effects (all differences exceeding 2 per cent were considered clinically significant) were observed between the disease-free and non-curative groups from week 12 onwards ($P < 0{\cdot}050$). A significant difference was found between the disease-free and recurrence groups at the end of follow-up at 144 weeks ($P = 0{\cdot}024$). The non-curative surgery and recurrence groups showed an identical pattern of HRQoL values (*Fig. 3*). The HRQoL of the group with recurrent disease was intermediate between that of the non-curative and curative surgery groups.

Separate analyses were performed within the recurrent disease group for patients whose recurrence was treated by further surgical intervention and those who received chemotherapy (*Fig. 4*). HRQoL in patients treated by further surgical resection was significantly better after 52 weeks than in the group receiving chemotherapy. EQ-5D™ VAS scores (patients' perception) showed a pattern for all clinical groups similar to that of the society-based EQ-5D™ values (data not shown).

Quality-adjusted life years

From the mean HRQoL values for each clinical state (*Table 2*), it was clear that the disease-free group fared better than the group that had non-curative surgery or those who developed recurrent disease. Furthermore, when surgical reintervention for recurrence seemed feasible, the HRQoL was comparable to that in the group in which no recurrence occurred. Separate analyses were performed to

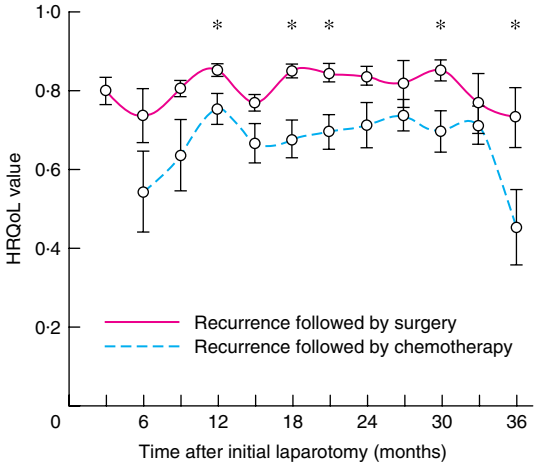


Fig. 4 Mean index value of patients' health calculated by the EuroQol – 5D for the subgroups with recurrent disease treated by (repeat) surgery or chemotherapy in the first 3 years after initial resection of hepatic colorectal metastases. The area under the curve corresponds to the number of quality-adjusted life years. Error bars represent standard errors. HRQoL, health-related quality-of-life. Asterisks indicate statistically significant effects ($P < 0{\cdot}050$), reported only if the number of observations exceeded ten (one-way ANOVA)

Table 2 Mean health-related quality-of-life values for each clinical state, as measured on the EuroQoL – 5D

State	Mean(s.d.) HRQoL	No. of observations	Maximum*	Minimum*
Death	0(0)	349	0	0
Disease-free	0·78(0·23)	891	0·92	−0·59
Non-curative	0·67(0·31)	162	0·92	−0·59
Recurrence	0·74(0·25)	450	0·92	−0·59
Without chemotherapy	0·82(0·17)	205	0·92	−0·43
With chemotherapy	0·68(0·28)	245	0·92	−0·59

*Scale is from 0 (death) to 1 (perfect health). HRQoL, health-related quality of life.

express the number of QALYs gained for each clinical state; the disease-free group accumulated 0·78 QALYs annually over 3 years, the non-curative group 0·67 QALYs annually and recurrence group 0·74 QALYs annually (*Table 2*). A total of 2·18 QALYs were collected in 3 years, whereas a total of 3·0 QALYs could theoretically have been achieved if all patients had been in perfect health for the 3-year duration of follow-up. Additionally, *Table 2* shows a difference of 14·0 per cent between recurrence subgroups, one treated with chemotherapy (0·68 QALYs) and the second surgically, without additional chemotherapy (0·82 QALYs).

Discussion

This paper describes the results of 3 years of global HRQoL measurement in patients who had initial surgical intervention for colorectal liver metastases and different subsequent treatments. Initially the patients showed a clear overall deterioration in HRQoL during the first weeks after surgery, in line with previous observations[12]. Thereafter, four distinct clinical health states were distinguished, each of which showed distinct patterns in terms of HRQoL outcome. Disease-free patients performed significantly better than patients who underwent non-curative surgery or patients with recurrent disease. The inferior HRQoL in patients with recurrent disease may be attributed to the knowledge of progressive disease as well as to the disease burden or administration of palliative chemotherapy. HRQoL outcomes combined with survival data (expressed as QALYs) showed that patients whose recurrence was treated surgically gained on average 14·0 per cent more QALYs during the 3-year study interval, which can be considered a substantial and clinically important health gain.

The present data showed a superior overall HRQoL in the first 3 years after surgical treatment of metastatic colorectal cancer compared with chemotherapy, which supports an aggressive surgical approach to colorectal liver metastases, when feasible. Furthermore, when recurrent disease was diagnosed, patients who underwent a second surgical intervention had a better HRQoL than those who were treated with chemotherapy. This supports an intensive follow-up scheme to detect recurrent metastatic disease at an early stage, thus maximizing the chance of resectability.

It was also observed that patients undergoing non-curative (futile) laparotomy had a significant deterioration in HRQoL, which did not recover to baseline. These data confirm earlier observations that non-curative laparotomy had a more severe impact on patients' well-being than primary denial of surgical treatment[12]. In the present study, the percentage of non-curative laparotomies (14·0 per cent) was similar to that reported in a recent multicentre study in a comparable patient group; 16·4 per cent of the latter patients did not undergo planned hepatic resection[21].

In the present study, no standard adjuvant chemotherapy was given after hepatic surgery. Data on overall and disease-free survival presented here are similar to those observed with no additional treatment in most recent studies

comparing adjuvant chemotherapy with no additional treatment[21,22]. Hence, the data on HRQoL in this series may be applicable to other studies as well.

The most commonly applied HRQoL instruments, such as the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy – G (and their modules), produce descriptive profile measures encompassing multiple health domains[23]. The same holds for supplementary modules of the EORTC QLQ-C30[24]. Instruments in this class are based predominantly on the classical test theory measurement model, which estimates the level of a health domain as the sum of responses to individual items[25]. Preferably, HRQoL measures should allow computational procedures and parametric statistical testing. This is facilitated when outcome measures are at least at the interval level[26], meaning that the metric of the HRQoL scale is continuous. In fact, the underlying rationale for the value-based HRQoL approach used in this study was to derive such qualified HRQoL measures. From a theoretical point of view, the value-based approach is more in line with measurement theories[27]. Until now, it has rarely been applied as an HRQoL measure in clinical studies, but used predominantly by health economists in the context of cost-effectiveness analysis. Yet the value-based HRQoL approach is conceptually identical to the index approach advocated by clinimetrics[28,29].

A drawback of the generic value-based HRQoL instruments is that they are all based on a limited set of health domains and often lack relevant domains for specific diseases. This may explain the recent interest in developing disease-specific value-based HRQoL instruments[5,30]. At present, it seems that generic value-based instruments and descriptive (profile) HRQoL measures are both necessary to discern the overall impact and the disease-specific domains that contribute to this. The present study can be regarded as an example of how these HRQoL instruments can assess the value of specific interventions in surgical oncology.

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Commentary

Long-term global quality of life in patients treated for colorectal liver metastases (*Br J Surg* 2011; 98: 565–571)

Surgery for colorectal liver metastases is becoming increasingly common, and surgeons need to understand the benefits and risks of resection from the patients' perspective when offering treatment. Obtaining information from well designed studies to inform patients fully of outcomes is difficult, however, because measurement of patients' views leads to additional complexities of data collection, analysis and interpretation. The present linked multicentre cohort study is an excellent example of how patient-reported outcomes can be used to evaluate surgery. Validated, brief health-related quality-of-life (HRQoL) measures were completed in hospital before surgery and distributed by post, with reminders during follow-up to ensure that data were reliable and compliance high. To avoid reporting bias and missing data, clinical and operative outcomes were documented prospectively using standard forms, and quality-adjusted life years (QALYs) were calculated to inform health policy.

The above factors ensure that the work is relevant to patients, surgeons and health policy makers, but several issues need elucidation. The study did not use a disease-specific measure of HRQoL, and problems such as postoperative fatigue may have been missed. Patients undergoing perioperative chemotherapy were not included and the impact of this on HRQoL remains unknown, although it is currently being addressed in the New EPOC trial[1]. The study did emphasize a HRQoL benefit from further resection of recurrent disease compared with administration of further chemotherapy, but randomized data are needed to make an unbiased comparison. Finally, for results to impact on clinical decision-making, it is necessary to communicate HRQoL data effectively to patients alongside clinical outcomes[2].

Whether it is possible to do this by providing information about HRQoL domains (such as symptoms or function) and survival data separately, or whether patients better understand a composite score of HRQoL and survival in the form of a QALY is unknown, and this needs addressing for these data to be used in a real life setting.

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